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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,845	11/19/2003	Ruth A, Gjerset	049146-1001	9478

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,845	GJERSET ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,24-29 and 31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24-29 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 6/30/08 was entered.

Claims 22, 24-29 and 31-39 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 24-29 and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. (US 5,747,469) in view of any one of Lu et al. (Cancer Res. 62:1305-1310, 01 March 2002), Tango et al. (Hum. Gene Ther. 13:1372-1382, 20 July 2002) or DePinho, R.A. (US 6,613,750), and Teimann, F. (WO 01/11063) and Dirks

et al. (US 6,060,273) for the same reasons already set forth in the Office action mailed on 1/29/08 (pages 2-10). ***The same rejection is restated below.***

Roth et al described recombinant viral vectors such as retrovirus, adenovirus, AAV, HSV, or recombinant CMV vectors or recombinant non-viral vectors in liposomal formulations that express p53; and methods of treating cancers (e.g., benign and metastatic or malignant tumor cells including epithelial tumor cells, lung carcinoma and breast cancer cells) in a patient by administering the recombinant vectors to cancer cells in combination with chemotherapy or radiation therapy (see at least Summary of the Invention in cols. 3-9; and issued claims).

Roth et al did not teach specifically a method of inducing killing or apoptosis or growth arrest of malignant or metastatic p53-positive cancer cells by contacting said cells with a bicistronic contruct comprising a single promoter controlling the expression of a sequence encoding p53 and a sequence encoding p14ARF.

At the effective filing date of the present application (12/17/2002), Lu et al disclosed that tumors without a p53 mutation often resistant to p53 gene therapy (see at least the abstract). Lu et al. disclosed that a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and the resultant inhibition and increased degradation of p53 mediated by MDM2 whose expression is induced by p53 but is inhibited by ARF (page 1307, col. 2 and page 1305, col. 1). Lu et al. showed that co-transfection with separate vectors encoding p14ARF and p53 was significantly more effective at inducing cell death in tumor cell lines (page 1306). Lu et al further taught that co-expression of p53 with

p14ARF in gene therapy will be more effective for tumors that have p53+ tumor cells (page 1309, col.1).

Tango et al also disclosed that co-transfection of human cancer cells both *in vitro* and *in vivo* with recombinant vectors (administered simultaneously) expressing p14ARF (human homolog of the mouse p19ARF) and p53 greatly enhances the tumoricidal effect of either p53 or ARF gene therapy alone as ectopic expression of ARF enhances the effectiveness of p53 gene therapy (see at least the abstract). Tango et al. taught that p14ARF induces p53 upregulation by neutralizing the effects of MDM2, a transcriptional target of p53 that antagonizes its function.

DePinho already taught a method of inhibiting the growth of tumor cells based upon the discovery of p19ARF acts as a suppressor of oncogenic transformation by binding to the MDM2 oncoprotein and blocking MDM2's ability to target associated proteins such as p53 and Rb, for proteosomal degradation, said method comprises administering to tumor cells an effective amount of p19ARF and p53 in various forms, including in the form of an expression vector (see at least Summary of the Invention; particularly col. 8, lines 6-53; and issued claims). DePinho also taught that p19ARF includes human p19ARF or p14ARF which is human homolog of the mouse p19ARF (col. 7, lines 7-55; and issued claims). DePinho further disclosed thatp19ARF acts in a p53-dependent manner to inhibit cellular transformation (see at least col. 18, lines 50-54).

None of Lu et al., Tango et al., and DePinho taught specifically that both p53 and p14ARF nucleic acid sequences are present in a biscistronic construct and under the expression control of a single promoter.

Also at the effective filing date of the present application, Tiemann already described at least bicistronic viral vectors, e.g., retrovirus or AAV or non-viral vectors for the treatment of malignant or metastatic cancers, e.g., liver, breast, lung, melanoma or prostate, comprising coding sequence for p53 and p14ARF under control of a single promoter and separated by an IRES; and use of the same (e.g., as a pharmaceutical composition) in treating cancers (see the entire reference, especially, in the translation, at pages 8-12, and claims 1, 3, 17-19 and 22-28). Tiemann also disclosed that treating tumor cells with both p53 and p14ARF genes resulted in synergistic killing of tumor cells (Figure 3).

Additionally, Dirks et al also taught the preparation and use of multicistronic expression units, including bicistronic units, containing a single transcriptional promoter (e.g., LTR, CMV, SV40), that allow the equimolar expression of the genes located in the corresponding cistrons (see at least the abstract and col. 5, line 22 continues to line 10 of col. 7). Dirks et al also noted the advantages of the disclosed multicistronic expression units over other alternatives including the use of multiple genes in separate expression vectors, multiple genes in independent transcription units on a vector or earlier versions of bicistronic or multicistronic vectors (see at least col. 1, line 21 continues to line 21 of col. 2).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Roth et al. by also using a recombinant vector co-expressing p14ARF gene and p53 under the control of a single promoter in the form of bicistronic expression units taught by Dirks et al for treating benign and/or metastatic or malignant tumor cells, including p53-positive cancer cells, in a patient in light of the teachings of any one of Lu et al., Tango et al. or DePinho, R.A., together with Teimann and Dirks et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because all of Lu et al., Tango et al. and DePinho taught that co-expression of p14ARF with p53 improved the effectiveness of p53 by blocking the inhibitory effects of MDM2 on p53. Moreover, Tienmann also taught that treating tumor cells with both p53 and p14ARF genes resulted in synergistic killing of tumor cells; and that these two genes can be present in a bicistronic vector construct. Furthermore, the bicistronic expression construct of Dirks et al allows the equimolar expression of the genes located in the corresponding cistrons and it offered various advantages over alternative approaches including the use of multiple genes in separate expression vectors (problems associated with this approach include the ratio of the expression of the different genes to each other depends both on the copy number and on the site of integration in the genome of the host cell together with the assumption that several plasmids copies are simultaneously taken up in a stable manner and continue to be harboured following division), multiple genes in independent transcription units on a vector (This approach is based on the assumption that mRNAs encode different proteins possess the same stability and translation efficiency) or earlier versions of

bicistronic or multicistronic vectors (the expression of the subsequent cistron is normally very low).

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Roth et al. with any one of Lu et al., Tango et al. or DePinho, R.A., and with Teimann, F. and Dirks et al.; coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 6/30/08 (pages 5-13) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue that the cited prior art provides no motivation to combine. With respect to the Lu et al and Tango et al references, Applicants argue that none of these references teaches or suggests a skilled artisan to construct a vector encoding both p53 and p14ARF under the control of a single vector for killing p53-positive cancer cells because both of these references detail experiments in which the levels of p53 and p14ARF are individually controlled (separate vectors). With respect to the DePinho reference, Applicants argue that the Examiner has failed to demonstrate that the teachings of DePinho suggest that exogenous p53 expression should be combined with

p14ARF in p53-positive cancer cells; and that this teaching does not materially expand on the teachings of Lu et al and Tango et al. With respect to the Tiemann reference, Applicants argue that Tiemann only suggests using these vectors for killing p53-negative cancer cells (Hep3B cells); and again the prior art fails to suggest the use of a single vector encoding p53 and p14ARF under the control of a single promoter for killing p53-positive cancer cells. With respect to the Dirks et al reference, nothing in this reference relates specifically to p53, p14ARF and/or their utility for killing p53-positive cancer cells. Applicants further argue that the Examiner has engaged in an impermissible hindsight reconstruction of Applicant's invention by alleging the Tiemann and/or Dirks et al motivate the use of Applicants' bicistronic vector for killing p53-positive cancer cells.

Firstly, it is noted that Applicants analyzed or considered the teachings of any one of Lu et al, Tango et al and DePinho references, Tiemnn and Dirks et al. in total isolation one from the others together with the teachings of the primary Roth et al reference. Moreover, the above rejection was made under 35 U.S.C. 103(a) and therefore, none of the cited references has to teach every limitation of the instant claims.

Secondly, as for applicants argument regarding that the cited references do not provide any suggestion or motivation to make the combination argued by the examiner, Examiner would like to recite a paragraph from *in re Oetiker,* 977, F.2d 1443, 1448 (Fed. Cir. 1992).

> "[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious

> within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teachings therein with another piece of prior art. This restrictive understanding of the concept of obviousness is clearly wrong…. While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, it is not necessary that the cited references or prior art specifically suggest making the combination…. In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to combine the prior art teachings is found in a specific reference."

Although, Roth et al did not teach specifically a method of inducing killing or apoptosis or growth arrest of malignant or metastatic p53-positive cancer cells by contacting said cells with a bicistronic contruct comprising a single promoter controlling the expression of a sequence encoding p53 and a sequence encoding p14ARF; at the effective filing date of the present application, **Lu et al. already disclosed that a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and the resultant inhibition and increased degradation of p53 mediated by MDM2 whose expression is induced by p53 but is inhibited by ARF. Lu et al further taught that co-expression of p53 with p14ARF in gene therapy will be more effective for tumors that have p53+ tumor cells**. Tango et al also disclosed that **co-transfection of human cancer cells both *in vitro* and *in vivo* with recombinant vectors (administered simultaneously) expressing p14ARF (human homolog of the mouse p19ARF) and p53 greatly enhances the tumoricidal effect of either p53 or ARF gene therapy alone as ectopic expression of ARF enhances the effectiveness of p53 gene therapy**; and p14ARF induces p53 upregulation by neutralizing the effects of MDM2, a transcriptional target of p53 that antagonizes its function. DePinho also taught a method of inhibiting

the growth of tumor cells based upon the discovery of p19ARF acts as a suppressor of oncogenic transformation by binding to the MDM2 oncoprotein and blocking MDM2's ability to target associated proteins such as p53 and Rb, for proteosomal degradation, and that **p19ARF acts in a p53-dependent manner to inhibit cellular transformation.** Additionally, Tiemann already described at least **bicistronic viral vectors, e.g., retrovirus or AAV or non-viral vectors for the treatment of malignant or metastatic cancers, e.g., liver, breast, lung, melanoma or prostate, comprising coding sequence for p53 and p14ARF under control of a single promoter and separated by an IRES**; **and that treating tumor cells with both p53 and p14ARF genes resulted in synergistic killing of tumor cells**. Dirks et al also taught **the preparation and use of multicistronic expression units, including bicistronic units, containing a single transcriptional promoter (e.g., LTR, CMV, SV40), that allow the equimolar expression of the genes located in the corresponding cistrons; and noted the advantages of the disclosed multicistronic expression units over other alternatives including the use of multiple genes in separate expression vectors, multiple genes in independent transcription units on a vector.** As already noted in the above rejection, an ordinary skilled artisan would have been motivated to carry out the modifications set forth above because all of Lu et al., Tango et al. and DePinho taught that co-expression of p14ARF with p53 improved the effectiveness of p53 by blocking the inhibitory effects of MDM2 on p53; **particularly it is known that a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells**.

Moreover, Tiemann also taught that **treating tumor cells with both p53 and p14ARF genes resulted in synergistic killing of tumor cells; and that these two genes can be present in a bicistronic vector construct. Furthermore, the bicistronic expression construct of Dirks et al allows the equimolar expression of the genes located in the corresponding cistrons and it offered various advantages over alternative approaches including the use of multiple genes in separate expression vectors (problems associated with this approach include the ratio of the expression of the different genes to each other depends both on the copy number and on the site of integration in the genome of the host cell together with the assumption that several plasmids copies are simultaneously taken up in a stable manner and continue to be harboured following division), multiple genes in independent transcription units on a vector** (This approach is based on the assumption that mRNAs encode different proteins possess the same stability and translation efficiency) or earlier versions of bicistronic or multicistronic vectors (the expression of the subsequent cistron is normally very low).

It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Thirdly, it should be noted that in the above rejection, anyone of Lu et al, Tango et al and DePinho references was used to supplement the primary teachings of Roth et al together with the teachings of Teimann and Dirks et al.

Fourthly, it should be noted that **the teachings of Teimann are not limited to treating only to Hep3B cells or p53-negative cancer cells**. Teimann taught clearly the use of bicistronic viral vectors for the treatment of malignant or metastatic cancers, e.g., **liver, breast, lung, melanoma or prostate**. It should be noted that **the instant claims are not necessarily limited to malignant or metastatic wild-type p53-positive cancer cells. In other words, the cancer cells may be positive for mutated p53**. The primary Roth et al reference already stated "Various mutant p53 alleles are known in which a single base substitution results in the synthesis of proteins that have quite different growth regulatory properties and, ultimately, lead to malignancies" (col. 2, lines 14-17); and "The overexpression of p53 in breast tumors has also been documented" (col. 2, lines 22-23)". Additionally, Roth et al clearly taught **a p53 gene therapy for treating cancers such as benign and metastatic or malignant tumor cells including epithelial tumor cells, lung carcinoma and breast cancer cells in a patient**. Furthermore, **not all cells (100% cells) in a human tumor are negative for wild-type p53 as evidenced at least by the teachings of Levine** (US 2003/0086935 with the effective filing date of at least 12/30/1994) who stated "More than 50% of human tumors contain cells expressing a mutant form of p53 gene. **In many tumors, one allele of the p53 gene contains a point mutation that encodes a mutant form of the protein while the other allele is partially or totally lost. This**

pattern is observed, for example, in approximately 70-80% of colon cancers, 50% of breast cancers, and 50% of lung cancers including 100% of small cell lung cancers" (paragraph 4).

2. Applicants argue that the cited prior art fails to provide a reasonable expectation of success for killing p53-positive cancer cells using a bicistronic vector encoding both a p53 and p14ARF under the control of a single promoter.

There is nothing that is unpredictable nor unreasonable for an ordinary skilled artisan to expect success for killing p53-positive cancer cells using a bicistronic vector encoding both a p53 and p14ARF under the control of a single promoter in light of the teachings of Roth et al. with any one of Lu et al., Tango et al. or DePinho, R.A., and with Teimann, F. and Dirks et al. as discussed above.

3. Applicants further argue that Applicants demonstrate surprising and unexpected results using the bicistronic construct for the treatment of p-53 positive cancer cells by referring to the Declaration of Dr. Gjerset submitted on October 31, 2007. Applicants argue that Dr. Gjerset demonstrated the unexpected finding that 10 moi of the bicistronic construct of p53 and p14ARF resulted in greater p53-positive cancer cell growth suppression than 200 moi of each individual vector used in combination; and interpolation of these results Dr. Gjerset concluded that approximately 5 moi of the bicistroinic vector had equivalent efficacy to the combination of about 200 moi of each individual vector and this represents a 40-fold increase in efficacy for the

bicistronic vector compared to what is predicted by a combination of the individual vectors. Applicants further argue that the Examiner's previous analysis of Dr. Gjerset's results is flawed for several reasons: (a) the same adenoviral vector is used for both bicistronic and monocistronic constructs; and the p53 and p14ARF mRNA transcribed from the adenoviral vector were under the control of the same CMV promoter; (b) the probability of cells to be infected with any adenoviral vectors either monocistronic or bicistronic construct is the same, not different as asserted by the Examiner. The examiner has not provided any evidence to substantiate any of the concerns raised and rendering these concerns an improper basis to entirely dismiss Dr. Gjerset's data.

Firstly, there is nothing unexpected or surprising **regarding to the highly effectiveness of the single promoter p53/p14ARF bicistronic vector relative to the dual vector system** at killing p53-positive cancer cells as demonstrated by the Declaration of Dr. Gjerset submitted on October 31, 2007. The advantages that are offered by a bicistronic expression vector relative to a dual vector system were already noted and recognized at least by Dirks et al. The bicistronic expression construct of Dirks et al allows **the equimolar expression of the genes located in the corresponding cistrons and it offered various advantages over alternative approaches including the use of multiple genes in separate expression vectors (problems associated with this approach include the ratio of the expression of the different genes to each other depends both on the copy number and on the site of integration in the genome of the host cell together with the assumption that several plasmids copies are simultaneously taken up in a stable manner and**

continue to be harboured following division), multiple genes in independent transcription units on a vector (This approach is based on the assumption that mRNAs encode different proteins possess the same stability and translation efficiency) or earlier versions of bicistronic or multicistronic vectors (the expression of the subsequent cistron is normally very low).

Secondly, please also note that **the instant claims are not limited only to the use of recombinant adenoviral particles at any particular moi for inducing killing or apoptosis of malignant or metastatic p53-positive cancer cells**. Therefore, the calculated 40-fold increase in efficacy for the bicistronic adenoviral vector may not necessarily be extrapolated to a bicistronic construct in other forms such as in the form of a plasmid vector or non-adenoviral vectors such as a retroviral vector. As already noted previously many factors favor the high efficacy rate for a bicistronic vector relative to a dual vector system, such as: (1) the dominace of one vector over the other in copy number as well as expression in transfected cells; (b) cellular uptake of at least two different vectors in a stable manner; (c) mRNAs encoding p53 and p14ARF resulted from two different vector constructs may not possess the same stability and translation efficiency (**for example incorporation of different vectors at different genomic sites for the dual vector system at least in the case of plasmid vectors and retroviral vectors**); (d) Cells already transfected with one vector may not have the same probability to be further transfected with another vector (same or different for the dual vector system) as untransfected cells. **These factors were already discussed by**

Dirks et al, please read the teachings of Dirks et al. particularly col. 1, line 21 continues to line 21 of col. 2.

Accordingly, claims 22, 24-29 and 31-39 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. in view of any one of Lu et al., Tango et al. or DePinho, R.A. (US 6,613,750); and Teimann, F. and Dirks et al. for the reasons set forth above.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633